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10/748,525	12/29/2003	Tae-Woong Koo	21058/0206735-US0	9348

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,525	KOO ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-26 and 28-34* is/are pending in the application.

4a) Of the above claim(s) *11-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10,24-26 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 7/23/2007.

The cancellation of claims 4 and 27 has rendered the 112-2nd paragraph rejection of these claims moot.

The amendment of the claims to recite, " an isolated population of labeled oligonucleotides" has overcome the 101 rejections of claims 1-3, 4-10, 24-26 and 28-34.

This action contains new grounds of rejection, including rejections of claims 3 and 26. As claims 3 and 26 were not previously rejected, this action is non-final.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 3 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated population of labeled oligonucleotides probes comprising an oligonucleotide associated with a series of detectably distinguishable molecules, the number and type of signal molecules identifying the nucleotide sequence of the probe, the number of probes in the population exceeding the number of unique signal molecules, wherein the type of nucleotide at each position in at least one of the labeled oligonucleotides probes is identified by an intensity of at least one of the unique signal molecules, does not reasonably provide enablement for wherein the number of unique signal molecules is equal to the number of nucleotides labeled of the oligonucleotide probe. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are drawn an isolated population of labeled oligonucleotides probes comprising an oligonucleotide associated with a series of detectably distinguishable molecules, the number and type of signal molecules identifying the nucleotide sequence of the probe, the number of probes in the population exceeding the number of unique signal molecules, wherein the type of nucleotide at each position in at least one of the labeled oligonucleotides probes is identified by an intensity of at least one of the unique signal molecule.

The claims further limit the number of unique signaling molecules to being present up to 4 times and the number of unique signal molecules is equal to the nmber of nucleotides of the labeled oligonucleotide probe.

The amount of direction or guidance

The specification provides no specific or substantial guidance to address the issue of labeling the nucleic acid with all four bases having a distinguishable label.. The specification does generically teach the method, but does not address this specific issue. The specification completely lacks guidance on labeling the nucleic acid with all four bases having a distinguishable label.

The presence of working examples

The specification thus teaches an example, but does not teach how to make the instant example.

The state of prior art and the predictability or unpredictability of the art:

Sauer et al (Journal of Biotechnology (2001) volume 86, pages 181-201) expressly teach that "A complete labeling (100% substitution with fluorescent dNTPs) of all four DNA-bases has not yet to be achieved (sic). Steric hindrance at the polymerase active site is supposed to prevent full replacement of natural dNTPs by the modified analogues (see page 188, column 2)." Since the current specification lacks any

guidance on how to overcome this art recognized problem, claim 3 and 26 is entirely unpredictable since the problem of steric hindrance prevents complete labeling.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to label every nucleotide of a polynucleotide with a different label. This would be replete with trial and error experimentation because the specification asserts the labeling of each nucleotide with up to 4 labels. However the specification nor the art teach how to label each nucleotide with a distinguishable label in such a way as to overcome the art recognized problem of steric hindrance inhibiting the labeling of every nucleotide or the suggested labeling of every nucleotide with multiple labels as suggested by the specification.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 1-2, 5, 7-9, 24-25, 28, 31, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Cronin et al (US patent 6,045,996, issued April 4, 2000).

With regards to claim 1, Cronin teaches an array of at least 500 different oligonucleotide features per square centimeter at discrete locations (see column 2, lines 23-27). These 500 oligonucleotides are a population of labeled oligonucleotide probes. Cronin further teaches labeling a target with luminescent dyes including polymethine dyes (see column 6, lines 12-22). Cronin further allowing hybridization and determining the identity of the probes to which they are labeled. The hybridization is labeling a probe. Cronin exemplifies this in the example. Cronin's hybridized array is a population of labeled oligonucleotides, comprising an oligonucleotide associated with the detectably distinguishable signal molecules (each labeled molecule is hybridized to a probe at a discrete location), the type and number of signaling molecules is less than the number of probes. As the nucleic acid sequence and location of the probes of Cronin's array are known, the detection of the label allows identification of the type of nucleotide at each position.

With regards to claim 2, Cronin teaches the target can be labeled at one nucleotide (see column 6 line 12). Cronin thus teaches the label is present once, which is less than 4 times.

The specification does not specifically define a reference signal molecule, but teaches an exemplary list in table 1, page 11.

With regards to claim 5, Cronin teaches fluorescein as a label. This is listed in the specification as an exemplary reference signal molecule. Cronin thus teaches probes labeled with reference intensity molecules.

With regards to claim 7 and 8, Cronin teaches the use of polymethine dyes, fluorescien, rhodamine, and so forth (column 6, lines 20-22). Cronin further teaches the use of Cy3 and Cy5 (see column 9, line 17). Cronin thus teaches oligonucleotide probes labeled with Raman labels, polymethine dyes and signal molecules from table 1.

With regards to claim 9, Cronin et al teaches the fluorescien, rhodamine, CY3, and Cy5 labels (see column 6, lines 20-22; column 9, line 17). Cronin thus teaches fluorescent dyes.

With regards to claim 24, Cronin teaches an array of at least 500 different oligonucleotide features per square centimeter at discrete locations (see column 2, lines 23-27). These 500 oligonucleotides are a population of labeled oligonucleotide probes. Cronin further teaches labeling a target with luminescent dyes including polymethine dyes (see column 6, lines 12-22). Cronin further allowing hybridization of the capture probe and target nucleotide and determining the identity of the probes to which they are labeled. The hybridization is labeling a probe. Cronin exemplifies this in the example. Cronin's hybridized array is a population of labeled oligonucleotides, comprising an oligonucleotide associated with the detectably distinguishable signal molecules (each labeled molecule is hybridized to a probe at a discrete location), the type and number of

signaling molecules is less than the number of probes. As the nucleic acid sequence and location of the probes of Cronin's array are known, the detection of the label allows identification of the type of nucleotide at each position.

With regards to claim 25, Cronin teaches the target can be labeled at one nucleotide (see column 6 line 12). Cronin thus teaches the label is present one, which is less than 4 times.

The specification does not specifically define a reference signal molecule, but teaches an exemplary list in table 1, page 11.

With regards to claim 28, Cronin teaches the fluorescein as a label. This is listed in the specification as an exemplary reference signal molecule. Cronin thus teaches probes labeled with reference intensity molecules.

With regards to claim 31 and 32, Cronin teaches the use of polymethine dyes, fluorescien, rhodamine, and so forth (column 6, lines 20-22). Cronin further teaches the use of Cy3 and Cy5 (see column 9, line 17). Cronin thus teaches oligonucleotide probes labeled with Raman labels, polymethine dyes and signal molecules from table 1.

With regards to claim 33, Cronin et al teaches the fluorescien, rhodamine CY3, and Cy5 labels (see column 6, lines 20-22; column 9, line 17). Cronin thus teaches fluorescent dyes.

Response to arguments

The response asserts that amending claims 1 and 24 to recite the limitations of claims 4 and 27 overcome the instant rejections. This argument has been thoroughly

reviewed, but is not considered persuasive because Cronin still anticipates the amended claim 1 and 24 as detailed above.

5. Claim 1,2, 5-10, 24, 25, 28-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Han et al (Nature Biotechnology (2001) volume 19, pages 631-635).

Han et al teaches a method of using multicolor optical coding for biological assays. Han teaches the use of 6 colors and 10 intensities could code for 1 million nucleic acid sequences (see abstract).

With regards to claim 1, Han further teaches the use of 3 colors and 10-intensities results in 999 codes (see page 631, 2nd column, 1st full paragraph). Han teaches in figure 5, 4 probes that are labeled with 3 different colors, which can be used to identify a nucleotide sequence.

With regards to claim 2, Han teaches in figure 5, the use of each label only once.

With regards to claim 5, Han et al teaches each labeled oligonucleotide probe is labeled with F by binding of the target nucleic acid (see figure 5).

With regards to claim 6, Han teaches probes of the same length, namely 14 nucleotides, in figure 5 which are from 10 to 50 nucleotides.

With regards to claim 7 and 8, Han teaches the use of adenine in the probes, represented by an A in the nucleotide sequences (see figure 6 and legend). As claim 8 depends from claim 7, the claims teach that adenine is a Raman label. Thus Han teaches Raman labels and signal molecules from table 1.

With regards to claim 9, Han et al teaches the use of quantum dots (see abstract).

With regards to claim 10, Han teaches the use of quantum dots, which are "zinc sulfide-capped cadmium selenide nanocrystals" (see abstract 2nd line). Han thus teaches the use of nanotags.

With regards to claim 24, Han further teaches the use of 3 colors and 10-intensities results in 999 codes (see page 631, 2nd column, 1st full paragraph). Han teaches in figure 5, 4 probes that are labeled with 3 different colors, which can be used to identify a nucleotide sequence. Han further teaches the labeled probes are hybridized to the to a complementary strand and are thus a reaction mixture.

With regards to claim 25, Han teaches in figure 5, the use of each label only once. Han thus teaches a reaction mixture with a target polynucleotide and a labeled probe, wherein each signal molecule is present once.

With regards to claim 28, Han et al teaches each labeled oligonucleotide probe is labeled with F by binding of the target nucleic acid (see figure 5). Han thus teaches a reaction mixture with a target polynucleotide and a labeled probe, wherein each signal molecule has an intensity reference signal.

With regards to claim 29 and 30, Han teaches probes of the same length in figure 5 and are from 10 to 50 nucleotides. Han thus teaches a reaction mixture with a target polynucleotide and a labeled probe, wherein each oligonucleotide is identical in length (claims 29 and 30) and length of 10 to 50 nucleotides.

With regards to claim 31 and 32, Han teaches the use of adenine in the probes, represented by an A in the nucleotide sequences (see figure 6 and legend). As claim 32 depends from claim 31, the claims teach that adenine is a Raman label. Thus Han

teaches Raman labels and signal molecules from table 1. Han thus teaches a reaction mixture with a target polynucleotide and a labeled probe, wherein each signal molecule is a Raman label or signal molecule from table 1.

With regards to claim 33, Han et al teaches the use of quantum dots (see abstract). Han thus teaches a reaction mixture with a target polynucleotide and a labeled probe, wherein each signal molecule is a quantum dot.

With regards to claim 34, Han teaches the use of quantum dots, which are "zinc sulfide-capped cadmium selenide nanocrystals" (see abstract 2nd line). Han thus teaches the use of nanotags.

Response to arguments

The response asserts that amending claims 1 and 24 to recite the limitations of claims 4 and 27 overcome the instant rejections. This argument has been thoroughly reviewed, but is not considered persuasive because Han still anticipates the amended claim 1 and 24 as detailed above.

6. Claims 1-3 and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Lockhart et al (WO97/27317, published July 31, 1997).

The specification does not specifically recite a definition for, "distinguishable label." The language "oligonucleotide associated with a series of detectably distinguishable signal molecules, the number and type of signal molecules identifying the nucleotide sequence of the probe" - does not specifically require that the nucleotide further comprises a label. Each base of the polynucleotide can thus be broadly interpreted as a distinguishable label, and any isolated probe population with each

nucleotide occurring less than 4 times broadly reads on the claim. Further each base can be further viewed as differentially labeled as isotopic differences in each base can be determined by mass spectroscopy.

With regards to claim 1, Lockhart et al teaches in figure 24, probe 1 ACTG and probe CTGT. Lockhart thus teaches an isolated population of labeled oligonucleotides associated with detectably distinguishable labels, wherein the type of each nucleotide at each position is identified by an intensity of at least one label.

With regards to claim 2, Lockhart teaches al teaches in figure 24, probe 1 ACTG and probe 2 CTGT. Each label occurs less than 4 times per labeled nucleotide.

With regards to claim 3, probes 1 and 2 of Lockhart each comprise 4 nucleotides, thus the number of unique sequences is equal to the number of nucleotides of the labeled oligonucleotide probes.

With regards to claim 24, Lockhart et al teaches in figure 24, probe 1 ACTG and probe CTGT. Lockhart teaches hybridization or target nucleic acids to arrays. Lockhart thus teaches a reaction mixture comprising isolated population of labeled oligonucleotides associated with detectably distinguishable labels, wherein the type of each nucleotide at each position is identified by an intensity of at least one label.

With regards to claim 25, Lockhart teaches al teaches in figure 24, probe 1 ACTG and probe 2 CTGT. Each label occurs less than 4 times per labeled nucleotide.

With regards to claim 26, probes 1 and 2 of Lockhart each comprise 4 nucleotides, thus the number of unique sequences is equal to the number of nucleotides of the labeled oligonucleotide probes.

Summary

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Carla Myers/
Primary Examiner, AU 1634